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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/249,220	02/12/1999	RICHARD A. MUELLER	SRL-6109	9695

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 04/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/249,220	MUELLER ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- *Extensions of time may be available under the provisions of* 37 CFR 1.136(a). *In no event, however, may a reply be timely filed* after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-27,60-63,69-72 and 151-153* is/are pending in the application.

4a) Of the above claim(s) *152 and 153* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25,26,60-62,69-71 and 151* is/are rejected.

7)☐ Claim(s) *27,63 and 72* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Claims 152 and 153 are drawn to species which were not elected. The elected species was nonyl-DNJ. In accordance with MPEP 803.02, since the method using nonyl-DNJ is now found allowable, the search will be extended. Claims 152 and 153 are drawn to non-elected species and are withdrawn from further consideration.

Claim Objections

2. The objection to the claims is withdrawn in view of the amendment.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

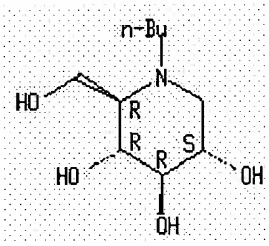
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 25, 26, 60-62, 69-71 and 151 are rejected under 35 U.S.C. 103(a) as being unpatentable over Block et al (WO 95/19172) in view of Partis et al (U.S. Patent 5,030,638).

Block teaches a method for treating a hepatitis virus infection in a mammal (see abstract) comprising:

(a) administering to said mammal an anti-hepatitis virus effective amount of at least one N-substituted-1,5, dideoxy 1,5-imino-D-glucitol compound (see page 17 and page 18, claim 1) of the formula below:

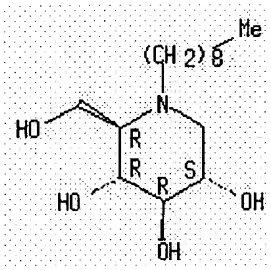


where R is a straight chain alkyl with four carbons and where W, X, Y and Z are hydrogen (see page 4 and page 18, claim 2).

With regard to the claims, and claims 61 and 70 in particular, Block teaches the pharmaceutically acceptable salt, HCL with the DNJ compound (see page 17, paragraph 2).

While Block expressly suggests that the size of the alkyl group can be modified, and teaches a range of 3 to 6 carbon atoms (see page 4, line 5), Block does not expressly teach the use of more than 6 carbon atoms as in the claims.

Partis teaches the use of longer chain DNJ molecules of the formula below, which is identical to the elected species, for treatment of viruses and motivates their use (see column 3, lines 31-55, for example).



Where R is a straight chain alkyl with nine carbons and where W, X, Y and Z are hydrogen (see columns 3 and 4).

With regard to claims 2, 3, 7, 9-11, 15, 17-19, 23, 25-27, 31, 33-35, 39, 60, 62, 63, 68, 69, 71, 72, 76, Partis teaches the nonyl DNJ (see column 3, lines 31-55).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the 3 to 6 carbon chain length of the alkyl DNJ compound used to treat hepatitis virus of Block by increasing the number of carbons in the chain to 9 since Partis teaches that the pharmacokinetics of nonyl-DNJ were superior to butyl DNJ. Partis specifically states,

> Although the lower alkyl derivatives of DNJ such as the N-methyl- and N-butyl-DNJ have been reported to have significant antiviral activity, it has been

surprisingly found that an enhanced spectrum of glucosidase enzyme inhibitory activity can be obtained in these derivatives by selectively increasing the alkyl chain length to at least 5 carbon atoms and up to about 10 carbon atoms. These higher N-alkyl derivatives of DNJ also have a longer in vivo half life than the lower C_1 -C_4 N-alkyl derivatives. (see column 3, lines 8-17)"

"In preliminary pharmacokinetic tests, the illustrative N-nonyl-DNJ surprisingly exhibited a half-life of 5 times that of the N-butyl-DNJ when administered in vivo in rats. That is, the N-nonyl-DNJ has a t1/2 in vivo in the rat of 6.24 hours when measured as total radioactivity in the blood compared to the t1/2 of N-butyl-DNJ which is only 1.24 hours. The longer half-life allows less frequent dosing of the mammal to maintain effective blood concentrations of the antiviral agent and prevents wide variations in blood levels. Less frequent drug administration should also reduce the gastrointestinal side effects seen with N-butyl-DNJ. Although the inventors

> are not to be bound by theory, it is believed that the increase in half-life
> may be partially due to increased lipophilicity and to increased chain length.
> Increased lipophilicity should allow increased penetration of the cell membrane
> and thus provide a higher intercellular concentration relative to surrounding
> body fluids."

Thus, an ordinary practitioner would have been motivated to use the higher N-alkyl derivatives, such as the 5-10 carbon atom length DNJ's of Partis in the place of the butyl DNJ of Block since Partis demonstrates that the higher N-alkyl derivatives of DNJ have a longer half life, which permits less frequent dosing, which should reduce gastrointestinal side effects and should be longer acting. Further, Partis notes that this will result in a higher intracellular concentration (see column 3, lines 30-50). Further, Partis notes that the higher chain alkyls have increased potency against the target enzyme and reduced IC-50 values, making them more active and effective (see column 3, lines 20-31). Further, MPEP 2144.09 notes "Compounds which are position isomers (compounds having the same radicals in physically different positions on the same nucleus) or homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by -CH2- groups) are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties." In this case, the broadest generic claim differs from Block only in the addition of a single CH2 group that is successively added to an alkyl chain. Partis teaches the desirability of such an addition and motivates the nonyl DNJ which is the elected species.

6. The rejection of claims 41-43, 47-52, and 56-58 under 35 U.S.C. 103(a) is moot in view of the cancellation of those claims.

Double Patenting

7. The rejection of claims 1-3,7-11,15-19,23-27,31-35,39-43,47-52,56-63 and 67-77 under the judicially created doctrine of obviousness-type double patenting is withdrawn in view of the amendment.

Allowable Subject Matter

8. Claims 27, 63, and 72 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

9. The following is a statement of reasons for the indication of allowable subject matter: Claims 27, 63 and 72 are limited to nonyl-DNJ in the treatment of hepatitis virus. While there is a prima facie case of obviousness with regard to this method, the data in the specification demonstrating a 2000 fold improvement in the efficacy of nonyl-DNJ relative to butyl-DNJ represents a secondary consideration, specifically an unexpected result, which overcomes the prima facie case of obviousness for this compound. A fivefold improvement would have been expected based upon the Partis reference, but the 2000 fold improvement represents an unexpected result which overcomes the prima facie case and renders the claims unobvious.

Response to Arguments

10. Applicant's arguments filed March 19, 2004 have been fully considered but they are not persuasive.

As noted above, Applicant's arguments were persuasive with regard to the nonyl-DNJ and the method limited to that compound is allowable. However, the broader claims, drawn to compounds with 7 carbons or more, are not found allowable since the unexpected result is not commensurate in scope with those claims.

Applicant begins the argument by noting that hepatitis virus and HIV are different viruses. The examiner was aware of this fact. The primary reference, Block, is drawn to treatment of Hepatitis virus, just as the claim is. The only obviousness issue is whether increasing the length of the alkyl chain in the DNJ molecule is obvious. Partis teaches that such a change improves kinetic properties in the patient, which would not change, irrespective of the virus with which the patient was infected. So Applicant's argument is not persuasive because it was known that multi length DNJ molecules were effective against Hepatitis virus and separately, it was known that increasing the chain length of DNJ molecules improve their pharmacokinetic properties. Thus, there was more than enough motivation to make this substitution.

Applicant's argument with regard to the belief of the inventor of the Block patent is entirely irrelevant and insignificant in this inquiry. First, the statement by the Applicant's attorney does not constitute evidence of any sort and is given NO probative value. Second, the obviousness issue is with respect to the combination with Partis, which provides express suggestion of the increased length.

11. Applicant's arguments with relation to Partis are not persuasive since they fail to combine the references. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually

where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Conclusion

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman
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Art Unit 1637